Prevention of Respiratory Failure Addressing COVID-19 Epidemic (PREFACE Trial)

CHEAT SHEET

Inclusion Criteria:

1. Males and Females 18 to 70 years of age
2. Lab confirmed COVID-19
3. Patients with progressive increase in supplemental oxygen requirements, developing acute hypoxic respiratory failure as defined by SaO2 < 93% on ≥6L supplemental oxygen.
4. Not on mechanical ventilation
5. D-Dimer > 1 µg/ml

Exclusion Criteria:

1. Active bleeding or high risk for bleeding (stroke within 14 days, gastrointestinal bleeding within 14 days, thrombocytopenia defined as platelet count <50 x103/µL, etc.)
2. Bleeding diathesis
3. Previously documented heparin induced thrombocytopenia
4. Patient on systemic anticoagulation for medical conditions which predate current admission: known prior VTE, atrial fibrillation, acute coronary syndrome.
5. If a patient is participating in any other clinical trial of an experimental treatment for COVID-19, the potential interaction of the trials will be reviewed by the study PIs for potential exclusion.
6. Pregnant females
7. Weight > 150 kg (rationale: enoxaparin dosing becomes less clear for patients greater than this weight)
8. Clinical contraindication as deemed by the attending physician

Prevention of **Re**spiratory **F**ailure **A**ddressing **C**OVID-19 **E**pidemic (**PREFACE Trial**)

Full protocol

Principle Investigators:

Sara Hegab, MD
Associate Director, Pulmonary Hypertension Program
Medical Director, Pulmonary Embolism Response Team (PERT)
Division of Pulmonary and Critical Care Medicine, Henry Ford Hospital
Assistant Professor, FTA
Wayne State University School of Medicine

Michael J. Simoff, MD, FACP, FCCP
Director, Bronchoscopy and Interventional Pulmonology
Director, Lung Cancer Screening Program
Pulmonary and Critical Care Medicine
Henry Ford Hospital
Professor of Medicine, FTA
Wayne State University School of Medicine

Co-Investigators:

Amy Tang, PhD
Assistant Scientist
Department, Public Health Sciences
Henry Ford Health System

Shane Bole
Data Specialist
Department, Public Health Sciences
Henry Ford Health System

Background:

Coronavirus disease 2019 (COVID-19) is a novel respiratory viral infection, with the first cases appearing in Wuhan, China in December 2019. Patients can be asymptomatic, have mild symptoms, have more significant symptoms requiring supplemental oxygen or develop severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), leading to acute respiratory distress syndrome (ARDS). The growing public health concern is the number of patients that develop SARS-CoV-2, many of which develop ARDS requiring mechanical ventilator support and critical care management. As would be expected, this is the population with the highest mortality rate.

In addition to the progression of lung disease, SARS-CoV-2 patients develop a viremia with systemic manifestations. Incubation is reported to be 1-14 days. The lungs, gastrointestinal tract, and heart appear to be the most susceptible organ systems to increasing viral load. At approximately 7-14 days after onset of symptoms, there is a reported increase in tissue expression of ACE-2, the entry receptor for SARS-CoV-2. With the currently understood natural history of the disease, lung parenchymal changes progress with worsening of pulmonary symptoms, peripheral blood lymphocyte counts drop, and a significant increase in inflammatory factors can be found. (1-4)

It is at this second phase of disease progression that patients develop a hypercoagulable state, with D-dimer based coagulation factors appearing abnormal. During the development of dyspnea and progression of chest imaging the measurements of D-dimer increased from mild to significant. Additionally, prolongation of the prothrombin time (PT) and decrease of fibrinogen (FBG) and platelets is noted. Observations that some of the non-survivors had developed ischemic changes including ecchymosis of fingers and toes at the same time as the organ functions of the heart and kidneys deteriorated. This pattern is consistent with the hypercoagulable phase of DIC. (5) It has been suggested that COVID-19 can activate coagulation cascade through various mechanisms, leading to severe hypercoagulability, potentiating the development of systemic microthrombi, leading to the injury of major organ systems. (6,7)

In an epidemiologic study in China evaluating the Wuhan population, the investigators found that 17% of patients developed ARDS. (8) Another retrospective evaluation in Wuhan, China of 109 patients who died of complications of SARS-CoV-2 versus 116 patients who survived, reported that 89.9% of those who died had developed ARDS versus 7.6% in the group that survived. (9) In another study, it was identified that the median time from admission to ARDS was two days. (10) Historically in the United states the mortality rates of ARDS are 25% to 40%. (11) The initial reports strongly suggest that the development of ARDS as a result of SARS-CoV-2 may have a higher mortality rate than ARDS due to different etiologies.

There is very little information regarding the histopathological features in COVID-19 infections. In one study two patients who both underwent lung resection for adenocarcinoma were later found to be COVID-19 positive after the operation. (12) Review of the histopathology demonstrated non-specific edema, pneumocyte hyperplasia, focal inflammation, and multinucleated giant cells (no hyaline membranes). In another report of a patient who had died of COVID-19, histopathologic evaluation of the lung tissue demonstrated findings of diffuse alveolar damage with exudates, with predominately lymphocytic inflammation, multinucleated giant cells, and large atypical pneumocytes. (13)

ARDS is an acute diffuse, inflammatory lung injury, leading to increased pulmonary vascular permeability, increased lung weight, and loss of aerated lung tissue with hypoxemia and bilateral radiographic opacities associated with increased venous admixture, increased physiological dead space and decreased lung compliance. (14) The

definition includes an acute onset (≤1 week), bilateral opacities consistent with pulmonary edema, a reduced PaO_2/FiO_2 (P/F) ratio (<100 severe, 100-200 moderate, 200-300 mild), not explained by fluid overload or congestive heart failure (CHF)

ARDS is the terminal path of various forms of lung injury. Pathologically this is observed as the development of alveolar injury due to diffuse alveolar damage. The cascade of events in the development and progression of ARDS causes the release of pro-inflammatory cytokines (tumor necrosis factor, interleukin (IL)-1, IL-6, IL-8). These events lead to recruitment of neutrophils to the lungs, which become activated with local of release toxic mediators (reactive oxygen species and proteases). This process causes damage of the capillary endothelium and alveolar epithelium leading to alveolar edema. (15) The progression of this process, leads to worsening impairment of gas exchange, decreased lung compliance, and increased pulmonary arterial pressure.

Lung compliance is the ability of the lung to stretch and expand. Pulmonary compliance (C_P) is defined as the change in lung volume per unit change in pressure.

$$C_P = \Delta V/\Delta P$$

ΔV = Change in lung volume
ΔP = Change in lung pressure

Lung compliance can be measured as either static (volume changed divided by the plateau inspiratory pressure) or dynamic (volume change divided by peak inspiratory transthoracic pressure). In the intensive care unit, the static lung compliance is most commonly evaluated for patient evaluation and management. A standard compliance curve is graphed as volume to pressure. When the volume of the lungs is maximized (overdistended) the airway pressure is significantly increased as is expected. When the volume is low (at functional residual volume/atelectasis), airway pressure is reduced. Normal ventilation takes place through normal tidal breathing.

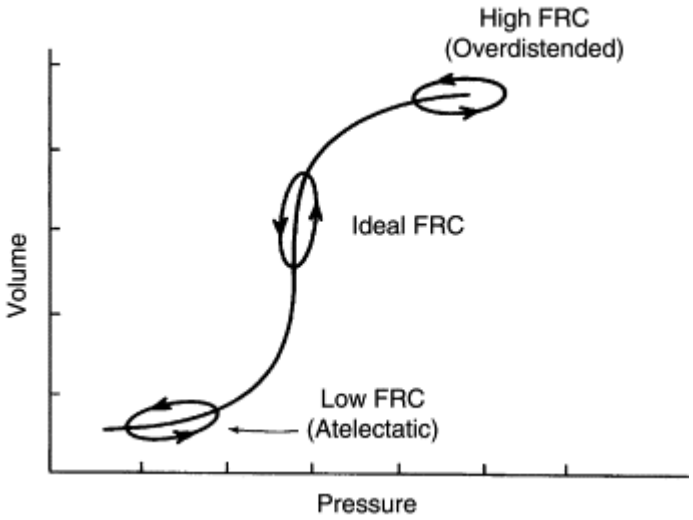

Figure from Respiratory physiology and Care, Wilson J, DiFiore JW. Pediatric Surgery (seventh Edition), 2012. Reproduced for research protocol without permission.

Diseased lungs, in which the compliance has dropped, leads to flattening of the compliance curve (overdistention) at much smaller volumes. Decreased lung compliance has strongly modified ventilation techniques, historically lung-protective strategies have developed for patients including moving to smaller and smaller tidal volumes with increased levels of positive end-expiratory pressure (PEEP).

In addition to traditional lung-protective strategies of ventilating with smaller lung volumes and higher PEEP pressure in ARDS, prone positioning of patients has been used successfully as a salvage therapy for refractory hypoxemia. Prone positioning was initially suggested to reduce atelectasis in the injured lungs, by reducing pleural pressure gradients and restoration of aeration to the recoverable dorsal lung segments. (16) There are multiple physiological processes, which occur in the lungs with prone positioning. In short, there is an improvement in ventilatory homogeneity through the lung in the prone position. Due to gravitational effects of pulmonary perfusion, improvement of the shunt fraction in patients proned increases by approximately 30%. (17,18,19) Prone positioning is recommended to be performed for 16 hours per day. When proned patients are returned to the supine position, the improvement in the PF ratio seen with prone positioning is reported to have prolonged benefit for at least four hours, with eventual return to the pre-proned condition. (20) There is anecdotal information in the literature and additionally through personal communications with treating physicians in Wuhan that there appears to be a significant benefit to oxygenation in patients with severe refractory hypoxemia using prone positioning.

Specific Aims:

1. To identify an intervention that may contribute to fewer patients developing severe refractory hypoxemia.
    a. Challenge: The current pandemic is causing a major stress to the medical establishment, leading to shortages of critical resources including by not limited to human, ventilators, hospital beds, and medications.
    b. Approach: The protocol will use standard medications that are currently not part of the management strategies of patients with COVID-19 infections.
    c. Impact: If the intervention provided at the suggested time works, fewer patients will develop severe refractory hypoxemia and respiratory failure potentially decreasing ventilator need, decreasing ICU bed utilization, and decreasing mortality.

Rationale for the Project:

1. It has been noted both in the Chinese experience as well as by local physicians that patients with active COVID-19 infections tend to develop a hypercoagulable state, with frequent clotting of lines, dialysis catheters, and the development of signs of systemic thrombotic/microthrombotic activity, demonstrating findings similar to the reports by Taisheng Li, et al (5).
2. The patients who develop ARDS by P/F ratio criteria are demonstrating an atypical physiologic finding of relatively normal lung compliance with severe hypoxemia. Interestingly the only histopathologic studies available (13) gives descriptions of diffuse alveolar damage but does not describe intra-alveolar hyaline cast deposition with the other specifically identified changes, which could conceivably explain the finding of more compliant lungs identified clinically.
3. Prone positioning in ARDS is an accepted salvage therapy for severe hypoxemia. Typically, patients demonstrate improvement in oxygenation in the prone position, which should lead to protection of this effect for $\geq$4 hours in most patients. It has been observed that once supine again, there is near immediate deterioration to the same level of severe hypoxemia identified prior to prone positioning in COVID-19 patients.
4. When patients are admitted to the hospital to receive supplemental oxygen or require ventilation, they are all positioned in the supine position. This would alter the lung physiology, with the most dependent lung zones becoming dorsal rather than basal.
5. We therefore suggest that due to the hypercoagulable state found in patients with COVID-19 infections, severe hypoxemia develops due to the progression of pulmonary vascular thrombotic/microthrombotic disease in the dependent lung zones, which in the predominately supine position seen in patients in the hospital, would be the dorsal zone of the lung. As this process progresses it causes shunt physiology, identified with worsening hypoxia and low P/F ratios. Additionally, this proposed pathologic change would account for the non-ARDS lung compliance patterns noted in most patients. Lastly, this mechanism would additionally explain the rapid deterioration of oxygenation in patients when returned to supine after prone positioning.

Significance:

Control / reversal of the suggested progressive thrombotic state found in patients with worsening hypoxia, respiratory failure, and ARDS, could lead to a disruption in the rapid clinical decline of patients with active COVID-19 infections interrupting the pathway of progressive hypoxic respiratory failure.

Subjects in the Project:

Inclusion Criteria non vented:

1. Males and Females 18 to 70 years of age
2. Lab confirmed COVID-19
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Exclusion Criteria:

1. Active bleeding or high risk for bleeding (stroke within 14 days, gastrointestinal bleeding within 14 days, thrombocytopenia defined as platelet count <50 $x10^{3/}$µL, etc.)
2. Bleeding diathesis
3. Previously documented heparin induced thrombocytopenia
4. Patient on systemic anticoagulation for medical conditions which predate current admission: known prior VTE, atrial fibrillation, acute coronary syndrome.
5. If a patient is participating in any other clinical trial of an experimental treatment for COVID-19, the potential interaction of the trials will be reviewed by the study PIs for potential exclusion.
6. Pregnant females
7. Weight > 150 kg (rationale: enoxaparin dosing becomes less clear for patients greater than this weight)
8. Clinical contraindication as deemed by the attending physician

Project Design and Protocol:

Open-label randomized controlled study with a 2:1 enrollment ratio of systemic anticoagulation using enoxaparin subcutaneous (or unfractionated heparin in those with a creatinine clearance (CrCl) <30 ml/m^2) in patients with COVID-19 and acute hypoxic respiratory failure.

Study Procedure:

1. Patients admitted to HFH with suspected/identified COVID-19 infection will be reviewed daily
2. Those patients that fulfill the inclusion / exclusion criteria will be approached regarding participation in the study. If the patient is intubated, their designated representative will be approached regarding participation in the study.
3. If after answering all questions they agree to participate, an Informed Consent Form will be signed with a copy provided to the patient or their representative.
4. After enrollment, participants will be randomly assigned in a 2:1 ratio to the intervention or standard care control arm. Randomization will be stratified by stable/non-stable status and creatine clearance rate, using sequentially numbered, opaque, sealed envelope (SNOSE) technique for the allocation concealment.
5. Once enrolled, the primary patient history and laboratories will be reviewed, and data collected.
6. Orders for Enoxaparin or high intensity unfractionated heparin IV will be started within six hours of enrollment:
    a. Options for stable patient (no procedures, hemodynamically stable):
        i. CrCl ≥ 30 mL/min: Enoxaparin 1 mg/kg Q 12 hours
        ii. CrCl of 15-29 mL/min: Enoxaparin 1 mg/kg Q 24 hours
        iii. CrCl < 15, rapidly fluctuating renal function, AKI/ESRD on IHD or CRRT: Heparin infusion at 12 units/kg/hr without initial bolus targeting aPTT 1.5-2.5 (55-75 seconds) normal range; dosing and monitoring per the HFH Low Intensity Heparin Protocol Guidelines. (21)
    b. Options for unstable patient (anticipated procedures, hemodynamically unstable, severe critically illness):
        i. Heparin infusion at 12 units/kg/hr without initial bolus targeting aPTT 1.5-2.5 (55-75 seconds) normal range
7. Duration of study anticoagulation:
    a. No acute venous thromboembolism: anticoagulation throughout hospital stay and for six weeks post discharge.
    b. New acute indication (DVT, PE, atrial fibrillation) for anticoagulation that develops during study treatment: 3 months; agent selection based on treatment team.
8. In the event of development of
    a. Suspected or confirmed heparin induced thrombocytopenia without thrombosis (isolated HIT): (22-25)
        i. Treat patient for 4 weeks with one of the following options given the clinical scenario:
            1. *Options for stable patient (no procedures, hemodynamically stable):*
                a. CrCl ≥ 30 and weight > 50 kg: Fondaparinox 2.5 mg SubQ Daily
                b. CrCl ≥ 30: Rivaroxaban 15 mg PO BID x 15 days, then 20 mg PO QD

c. CrCl < 30: Apixaban 5 mg PO BID

2. *Option for unstable patients (anticipated procedures, hemodynamically unstable, severe critically illness):*

a. Bivalirudin – goal PTT 1.5-2.5 times baseline PTT; dosing and monitoring per the HFHS HIT Guidelines. (Appendix A)
   i. CrCl >60 mL/minute: 0.15 mg/kg/hr
   ii. CrCl 30 to 60 mL/minute: 0.08 mg/kg/hr
   iii. CrCl <30 mL/minute or dialysis: 0.05 mg/kg/hr
   iv. CRRT: 0.07 mg/kg/hr

b. <u>Suspected or confirmed heparin induced thrombocytopenia with thrombosis (HITT):</u>
   i. Treat patient for 3 months with one of the following options given the clinical scenario:
      1. *Stable patients (no procedures, hemodynamically stable):*
         a. CrCl < 30: Apixaban 10 mg PO BID, then Apixaban 5 mg PO BID thereafter
         b. CrCl ≥ 30: Fondaparinox
            i. Weight < 50 kg: 5 mg SubQ Daily
            ii. Weight 50-100 kg: 7.5 mg SubQ Daily
            iii. Weight > 100 kg: 10 mg SubQ Daily
         c. CrCl ≥ 30: Rivaroxaban 15 mg PO BID x 15 days, then 20 mg PO QD
      2. *Unstable patients (anticipated procedures, hemodynamically unstable, severe critically illness):*
         a. Bivalirudin: goal PTT 1.5-2.5 times baseline PTT; dosing and monitoring per the HFHS HIT Guidelines
            i. CrCl >60 mL/minute: 0.15 mg/kg/hr
            ii. CrCl 30 to 60 mL/minute: 0.08 mg/kg/hr
            iii. CrCl <30 mL/minute or dialysis: 0.05 mg/kg/hr
            iv. CRRT: 0.07 mg/kg/hr

9. The patients will be monitored after the initiation of therapy.
   a. The first follow-up will be twelve hours after the start of anticoagulation.
   b. Evaluation of clinical status will be completed twice daily to monitor progression of hypoxemia, respiratory failure, development of ARDS.
   c. Daily laboratory testing including CBC with differential, electrolytes, PT, aPTT, INR, D-Dimer.
   d. Ferritin, LDH, Triglycerides will be checked QOD as per Henry Ford Hospital COVID-19 Management guidelines.
10. All patients who are in the control group will receive standard of care therapy inclusive of VTE prophylaxis and proning if part of routine care.

11. Post-discharge follow-up:
    a. Patients will be maintained on anticoagulation upon discharge.
    b. Patient contact 2 weeks post discharge
    c. D-Dimer to be drawn at 4 weeks
    d. Patient contact 6 weeks post discharge
        i. If D-Dimer remains elevated, discussion regarding continuation of anticoagulation vs. evaluation of VTE.

Outcomes:

1. Primary Endpoint:
    a. Progression to require mechanical ventilation

2. Secondary Endpoints:
    a. Day 28 all-cause mortality
    b. Ventilator days
    c. ICU days
    d. Central catheter thrombotic events
    e. Diagnosed VTE

3. Exploratory Endpoints:
    a. Change in D-Dimer
    b. Change in Ferritin
    c. Change in CRP
    d. Change in LDH
    e. Change in Triglycerides

Adverse Events:

Patients will be followed for 28 days during which time. All adverse events (AE) and serious adverse events (SAE) will be recorded including, but not limited to:

1. Minor Bleeding: Any sign or symptom of hemorrhage (i.e., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for the definition of major bleeding but does meet at least one of the following criteria:
    i. requiring medical intervention by a healthcare professional
    ii. leading to hospitalization or increased level of care
    iii. prompting a face to face (i.e., not just a telephone or electronic communication) evaluation (26)
2. Major bleeding: Bleeding in non-surgical patients is defined as having a symptomatic presentation and 1:
    i. Fatal bleeding, and/or
    ii. Bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or
    iii. Bleeding causing a fall in hemoglobin level of 20 g L^{-1} (1.24 mmol L^{-1}) or more, or leading to transfusion of two or more units of whole blood or red cells. (26)
3. Thrombocytopenia (Heparin induced)

Data Collection:

1. Baseline characteristics:
    a. Demographics: Age (years), Gender, Height, Weight, Race/Ethnicity
    b. Comorbidities
    c. Preadmission Medications

2. Laboratory evaluation:
    a. CBC, PT, aPTT, INR, D-Dimer, electrolytes, creatinine clearance, LDH, ferritin, triglycerides, high sensitivity troponin, fibrinogen, anti-thrombin III activity, SOFA score

3. Clinical evaluation (twice daily measurements)
    a. Patients not intubated
        i. COVID-19 therapy (azithromycin, hydroxychloroquine, solumedrol, etc.)
        ii. Modified Borg score with visual analog
        iii. Amount of supplemental oxygen
        iv. Oxygen saturations
        v. Notation of awake prone positioning

vi. Previous clotting event of central venous access or peripheral arterial access

b. Ventilated Patients
   i. COVID-19 therapy (azithromycin, hydroxychloroquine, solumedrol, etc.)
   ii. FiO2
   iii. PEEP
   iv. SaO2
   v. P/F Ratio
   vi. Static lung compliance
   vii. Notation of prone positioning
   viii. Volume status
   ix. SOFA score
   x. Previous clotting event of central venous access or peripheral arterial access

4. Radiographic imaging
   a. CT or chest radiograph reports will be collected and temporally related to point of admission to study. Subsequent imaging will be based on clinical requirements.

ISHT SIC Score

Variable	Value	Points
Platelets, K/µL	>100	0
	50-100	1
	<50	2
INR	<1.3	0
	1.3-1.7	1
	>1.7	2
D-Dimer, ng/mL	<400	0
	400-4000	2
	>4000	3
Fibrinogen, mg/dL	>100	0
	<100	1

Data Analysis:

All statistical analyses will be conducted according to the intention-to-treat principle. Thus, patients will be analyzed according to the arm to which they were allocated.

Data will be summarized by intervention arms using bivariate analyses. All hypothesis testing will be carried out at the 5% (2-sided) significance level unless otherwise specified. We will report the number and percentage of primary outcome. To assess the intervention effect, logistic regression models, generalized linear models, Kaplan Meier plots and Cox proportional hazard models will be performed for both primary and secondary outcomes, as appropriate.

Descriptive analyses will be performed for the exploratory outcomes.

An interim safety analysis is will be performed upon recruitment of patient 329.

Justification for Number of Subjects or Data:

Sample size estimate suggest that 1031 participants are required.

The primary outcome measure for the power calculation is the difference of intubation rate between intervention arm (systemic anticoagulation using enoxaparin subcutaneous (or unfractionated heparin) and control arm (current standard care). We expect the intervention arm will provide a reduction by 30%. The baseline intubation rate was estimated 25 % in the control arm. Assuming alpha at two-sided 0.05 and power at 80% indicates that a total sample size of 1031participants (687 in the intervention and 344 in the control arm) would be required.

Required sample sizes **Assuming 80% power, alpha=0.05 and two-sided testing**	
Reduced by	**Estimated intubation rate in COVID-19 inpatients with standard care**
	25%
10%	10181 (6787:3394)
20%	2435 (1623:812)
30%	1031 (687:344)
40%	548 (365:183)
50%	329 (219:110)

Randomization

Participants will be randomly assigned in a 2:1 ratio to the intervention or standard care control arm. Randomization will be stratified by stable/non-stable status and creatine clearance rate. The allocation sequence will be generated using random permuted blocks within stratum. Using restricted randomization within the stratum ensures that number of participants is balanced between study arms within stratum and the stratification factors will be balanced in each study arm.

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Appendix 1:

HFHS – Tier 1: Heparin Induced Thrombocytopenia (HIT) Guidelines -(MMC-08): Bivalirudin Criteria for use in patients with suspected or confirmed HIT.

Dosing for HIT

Therapeutic Range (goal) of the aPTT Value:

- The therapeutic range is an aPTT value 1.5-2.5 times the patient's baseline aPTT value.
- If no baseline aPTT value is available, use 29 seconds as the baseline value.
- The upper range should not exceed 100 seconds.

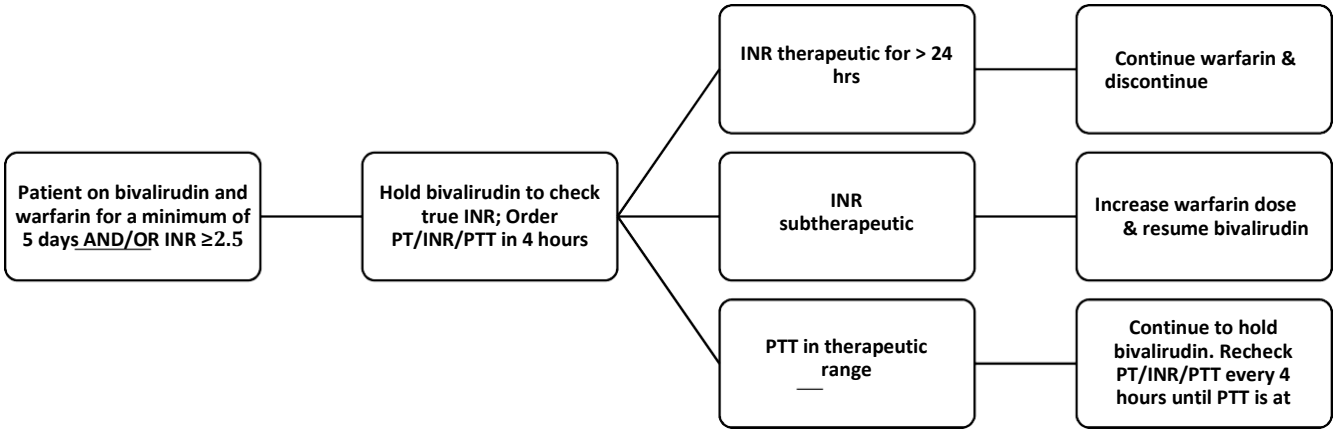
Table 1. Bivalrudin initial dosing

Bivalirudin Initial Dosing (250 mg/50 mL NS or D5W)		**Monitoring**
CrCL (ml/min)	**Dose (mg/kg/hr) – based on actual weight. Max: 150 kg**	
> 60	0.15 mg/kg/hr	Draw first aPTT 2 hours after the initiation of the infusion.
30 - 60	0.08 mg/kg/hr	
< 30/iHD	0.05 mg/kg/hr	
CRRT	0.07 mg/kg/hr	

Table 2. Bivalirudin maintenance infusion dose adjustment

PTT (seconds)	**Dose Adjustment**	**Monitoring**
< 1.5 x baseline	Increase infusion by 20%	Recheck PTT 2 hours after rate change
1.5 – 2.5 x baseline	Continue current rate	Recheck PTT in 4 hrs; if within therapeutic range 2 consecutive times, check PTT every 12 hrs
> 2.5 – 3 x baseline	Decrease infusion by 20%	Recheck PTT 2 hrs after rate change
> 3 x baseline	Hold for 1 hour, then restart at 50% lower rate	Recheck PTT 2 hrs after rate change

Figure 1. Transitioning to warfarin: Bivalirudin conversion to warfarin



- Due to the affinity for thrombin, all DTI interfere with functional clotting assays (PT/INR). Among the commercially available DTI's the prolongation of the INR by bivalirudin is less that seen with that of argatroban.10 Evidence suggests that bivalirudin's effects INR by elevating it by approximately 0.5 over the course of therapy initiation and decreases the INR by 0.5 on bivalirudin discontinuation. (11)
- In order to predict the INR on warfarin alone, temporarily discontinue bivalirudin until its anticoagulant effect has resolved (usually for 4 to 6 hours or until the PTT is returned to baseline) then follow Figure 1.
- If the repeat INR is below the desired therapeutic range, resume the infusion of bivalirudin and adjust warfarin dose accordingly; Repeat the procedure daily until the desired therapeutic range on warfarin alone is reached.

Table 3. Transitioning between parenteral anticoagulants in HIT/HITTS

From	To	Action
Fondaparinux Therapeutic dose	Bivalirudin	• Discontinue fondaparinux • Initiate bivalirudin when next fondaparinux dose is expected to be given (24 hours from last given dose)
Fondaparinux Prophylactic dose	Bivalirudin	• Discontinue fondaparinux • Initiate bivalirudin as clinically indicated irrespective of time of last given fondaparinux dose
Bivalirudin Without renal	Fondaparinux	• Discontinue bivalirudin drip • Initiate fondaparinux immediately
Bivalirudin With renal impairment	Fondaparinux	• Discontinue bivalirudin drip • Initiate fondaparinux once PTT is 2 times the baseline

Table 4. Transitioning from bivalirudin to DOAC in HIT/HITTS

From	To	Ac
Bivalirudin Without renal impairment	DOAC	• Stop bivalirudin drip • Start DOAC immediately

Bivalirudin With renal impairment		• Exercise caution regarding the use of DOACs in patients with renal impairment • Selection of DOAC agent is not recommended for patients with severe renal impairment

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